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Falling admissions to hospital with febrile seizures in the UK

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ABSTRACT

Objectives. There was a reduction in febrile seizure admissions in Scotland after 2008. Our hypothesis was that a similar trend would be seen in other countries.

Methods. We obtained the number of febrile and non-febrile seizure admissions in England and Scotland 2000-2013 and trends in incidence of all seizure admissions 2000-2013 in European countries. We compared the incidence of admission for febrile seizure (Scotland and England) and all seizures (all countries) between 2000-2008 and 2009-2013, and also before and after introduction of routine pneumococcal vaccination.

Results. The incidence of febrile seizure admissions/1000 children in 2009-2013 was lower than 2000-2008 in Scotland (0.79 versus 1.08 $p=0.001$) and England (0.92 versus 1.20 $p<0.001$). The incidence of all seizure admissions (but not non-febrile seizures) was lower in 2009-2013 compared to 2000-2008 in Scotland (1.84 versus 2.20 $p=0.010$) and England (2.71 versus 2.91, $p=0.001$). Across 12 European countries (including the UK) there was no difference in all seizure admissions after 2008. We explored the possibility that the fall was related to the introduction of routine pneumococcal vaccination but there were insufficient data.

Conclusion. A fall in admissions for febrile (but not afebrile) seizures after 2008 in Scotland and England explains a fall in all seizure admissions. A fall in all seizures has not occurred in other European countries, and more research is required to understand the different outcomes in the UK and non-UK countries.

Key words: Child, epidemiology, febrile seizures, hospital admission

INTRODUCTION

A febrile seizure (FS) is a common condition defined as ‘an epileptic seizure occurring in childhood after one month of age, associated with a febrile illness that is not caused by an infection of the central nervous system’ and has a peak incidence at 18 months[1]. Studies in the United States, South America, and Western Europe have found that between 2.2% and 5% of all children experience at least one FS before the age of 5[2,3] and the incidence is considerably higher in other populations, for example 7% in Japan, 14% in Guam[4]. There is a genetic predisposition to febrile seizures and a child of two parents with a history of febrile seizures has a one-in-three chance of having a febrile seizure themselves [5]. Any febrile illness can potentially trigger a febrile seizure before the age of five years and human herpes virus 6 is thought to be a common cause[6].

The number of annual emergency medical paediatric admissions in both England and Scotland is increasing[7,8] and FS are one of the most common reasons for zero day emergency hospital admission (i.e. where the child is admitted and discharged on the same day)[7]. The contribution of seizures to hospital admissions is not clear. A recent publication has observed a rise in elective but not emergency admissions for epilepsy in Scotland [9]. A study from the Nuffield Trust[10] noted that the number of admissions for all seizures in children had fallen between 2005/6 and 2015/16, but this study[10] did not report febrile and non-febrile seizures separately so the relative contribution of each could not be determined. Two of the authors (JS and ST) happened to notice a fall in FS after 2008 whilst looking at trends in FS over time as part of JS’s research interest

Here we describe work which extended this unexpected finding and addressed three questions: Was there a commensurate fall in FS admissions in England after 2008?; Was the fall in all seizure admissions [10] due to a fall in both FS and on FS admissions?; and has there been a fall in FS and all seizure admissions in non-UK countries? Finally we sought to identify why there may have been a fall in the incidence of FS admissions after 2008.

Materials and Methods

Study design. This was a study of secular trends in admissions to hospital with FS and all seizures in children using routinely acquired whole-population data from Scotland, England and other European countries.

Definitions. The definition of a FS admission was one with the ICD-10 code R56.0 [“febrile convulsions”]. Non-febrile seizure admissions occurred if the following codes were present: G40.9 [“epilepsy unspecified”], R56.8 [“unspecified convulsion”] or G40.3 [“Generalized idiopathic epilepsy and epileptic syndromes”]. Other ICD-10 codes for non-febrile seizures (e.g. G40.0, G40.1, G40.2 and G40.4 through to G40.8) comprise 8% of all non-febrile seizures (and include focal seizures) in the ISD data and were not included. Changes in diagnostic and/or coding practice are a recognised cause for apparent sudden falls in hospital admissions for one diagnosis[11] and to address this we also described trends in rigors (defined as admission code R50.9 [“fever with chills”]); this approach would identify whether the fall in FS may be explained by a rise in rigors.

Scotland hospital admission data (ISD). Anonymised details of all admissions to Scottish hospitals for individuals aged ≤ 16 years between January 1, 2000 and December 31, 2013 were provided by the Information Services Division (ISD) of the Scottish Government, as previously described[7]. Information included the primary diagnosis (using the International Classification of Disease, ICD-10 coding), age (in years and months), sex, diagnosis, socioeconomic status (Scottish Index of Multiple Deprivation, SIMD, where the population is evenly distributed across quintiles and where 1 is the least affluent quintile). Elective admissions, i.e. non-urgent admissions which was planned several days before the admission, were removed from the dataset prior to analysis. Population estimates from the National Records of Scotland, which provide an annual breakdown of the Scottish paediatric population between 2000-2013, were used to standardise number of admissions to 1000 population aged ≤ 16 years [12].

England admission data (Hospital Episode Statistics, HES)[13]

The number of admissions for febrile and non-febrile convulsions and fever with child (R50.6) in England was standardised for the population size (per 1000 children aged ≤ 14 years) for mid-2000 to mid-2013 using data from the Office of National Statistics (ONS, [14]).

European data (World Health Organisation data, WHO) [15]

The option "Comparisons between countries for one selected disease" was selected to obtain a list of 32 European countries, and from this data from countries who used ICD-10 coding for hospital admissions was extracted (Diagnosis/18/R56). The ICD-10 coding in this data source is only to two digits and we obtained the proportion of children per 1000 admitted per annum with ICD-10 code R56- (i.e. we could not distinguish FS from non-febrile seizures). Data from 0-1 year olds and 1-4 year olds were extracted.

Analysis Trends in admissions per 1000 population between 2000 and 2013 were presented graphically for febrile and non-febrile seizures for Scotland and England. The number of year's data was relatively small (especially for some European countries) and we applied a pragmatic approach comparing mean admission incidence between "before" (i.e. 2000-2008) and "after" (i.e. "2009-2013) the introduction of a factor potentially causally related to the fall in FS admissions. Student's t test used to analyse the difference in mean incidence of admissions for febrile and non-febrile seizures (separately) and all seizures (i.e. febrile and afebrile seizures) between these periods in Scotland and England. We then used general estimating equations (GEE, Auto regressive 1 model) to analyse the difference in incidence of FS admissions in European countries before and after a given point in time. Standard statistical software was used (IBM SPSS release 24.0.0.0) and a p value of <0.05 was considered significant.

Ethics. Permission to use the ISD data was obtained from the Public Benefit and Privacy Panel for Health and Social Care (the Caldicott guardian for NHS Scotland) and the North of Scotland Research Ethics Committee. Ethics approval was not sought to use the publically available HES and WHO data.

RESULTS

Results from Information Services Division, Scotland

There were 570,403 emergency medical paediatric admissions between 2000 and 2013, of which 13,671 were for FS, 15,261 for non-febrile seizures and 7,265 were for fever with chills. The median age on admission for FS was 1.75 [IQR 1.25, 2.67] years, compared to a median age of 5.0 [IQR 1.83, 10.0] years for non-febrile seizures and a median age of 1.58 years [IQR 0.58, 3.67] for fever with chills. The proportion of children with more than one admission with FS between 2000 and 2013 remained stable (supplement table one). 56% of FS admissions were male, and 54% for admissions with non-febrile seizure or fever with chills were male. The incidence of FS admissions rose from 0.93/1000 in 2000 to a peak of 1.17/1000 in 2008 and then fell to 0.71/1000 in 2013, table one and figure one. The mean (SD) incidence/1000 of FS admissions was 1.08 (0.10) for the 2000-2008 period and was 0.79(0.15) for the 2009-2013 period, $p=0.001$. There was no difference in incidence of non-FS admissions/1000 between the periods 2000-2008 [1.11 (0.13)] and 2009-2013 [1.06 (0.08)] $p=0.398$. The mean (SD) incidence of admissions coded as fever with chills was 0.18/1000 (0.06) for 2000-2008 and was 0.016 (0.07) for the era 2009-2013, $p=0.203$. Admission for fever with chills reached a peak in 2009. The mean incidence/1000 of admissions was 0.47 (0.18) for 2000-2008 and 0.61 (0.16) for 2009-2013, $p=0.170$. The mean (SD) incidence of admission/1000 with all seizures (i.e. febrile and non-febrile seizures combined) was 2.20 (0.21) for 2000-2008 and 1.84 (0.21) for 2009-2013, $p=0.010$.

Results from Hospital Episode Statistics, England

The total number of admissions with seizures between 2000/01 and 2013/14 was 368,989 including 142,572 with febrile seizures and 226,417 with non-febrile seizures. The incidence of FS admissions remained static between 2000/01 and 2008/9 at approximately 1.20/1000 and the fell to 0.87/1000 in 2013/14, figure one. The mean (SD) incidence of FS admissions/1000 in 2000/01-2008/09 was 1.20 (0.06) and fell to 0.92 (0.03) for 2009/10-2013/14 $p<0.001$; the incidences of non-febrile seizure

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3 admissions in the corresponding periods were 1.71 (0.11) and 1.80 (0.01) $p=0.132$. The mean (SD)
4 incidences of admissions for febrile plus non-febrile seizure admissions for 2000/01-2008/09 and
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6 2009/10-2013/14 were 2.91 (0.10) and 2.71 (0.03) respectively, $p=0.001$.
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11 **Results from WHO data, Europe**

12 Data from 13 countries was included. There was a fall in incidence of all seizure admissions in the
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14 Finland, Poland, Slovenia, Slovakia and the UK after 2008 but not in Croatia, Cyprus, Latvia, Lithuania,
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16 Luxembourg and Malta, figure two table two; in the general estimating equation there was no
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18 significant change in seizure admissions/1000 (mean reduction for 2009-2013 compared to 2000-2008
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20 0.29 [95% CI -0.25, 0.84] $p=0.0288$). The absolute values of admission prevalence are provided in
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22 supplemental table two.
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30 **Possible mechanism for falling FS admissions**

31 Routine pneumococcal vaccination in 2006 was identified as a possible mechanism for falling FS
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33 admissions. The only other new vaccination introduced in the UK was human papilloma virus
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35 vaccination in adolescent girls (2008). There were no data to indicate whether HHV6 prevalence or
36
37 virulence had changed prior to 2008. Routine pneumococcal vaccination was introduced in the
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39 following countries sufficiently early to allow meaningful analysis: Cyprus (vaccination introduced
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41 2008), Luxemburg (2003), Switzerland (2006) and UK (2006) [16]. In the general estimating equation
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43 there was a non-significant fall in seizure admission incidence/1000 with a three year lag after
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45 pneumococcal vaccination was introduced (0.46 [95% CI -0.18, 1.09] $p=0.157$). The incidence of
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47 seizure admission was higher after 2009 in the four countries who did not introduce pneumococcal
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49 vaccination compared to the period up to an including 2008 (supplemental table three).
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DISCUSSION

This study was designed to extend to other countries our observation that there had been a fall in FS admissions in Scotland after 2008. The answers to our three questions were that: (i) FS admission incidence fell across England for the period 2009-2013 compared to 2000-2008 (ii) the incidence of admissions for all seizures in Scotland and England was lower for 2009-2013 compared to 2000-2008 but there was no fall in the incidence of non-febrile seizure admissions (iii) there was no consistent evidence of a fall in all seizure admissions after 2008 across the European countries studied. There were insufficient data available to determine whether the introduction of routine infant pneumococcal vaccination was temporally related to a subsequent fall in seizure admissions. Collectively these findings mean that there has been a fall in febrile seizure admissions in the UK but not other European countries and we cannot explain why this fall has occurred.

This is the first study of which we are aware to explore secular trends in admission incidence for FS in children. Our findings are consistent with an earlier report of a fall in all seizure admissions in England when comparing the years 2006/7 and 2015/16 using Hospital Episode Statistics [10], and here we extend these findings by describing how the fall is also seen in Scotland, is explained by a fall in febrile seizures and that the drop is not seen in other continental European countries. There is internal consistency in our findings since the fall in FS admissions between 2000-2008 and 2009-2013 is approximately 25% in Scotland and England.

FS admission data in other European countries were not available to allow direct comparison with results in Scotland and England and we used details of all seizure admissions as a proxy for febrile seizure admissions. With this approach, the fall in all seizures seen in Scotland and England after 2008 was not apparent in other countries. We are confident that in contrast to the UK there has not been an overall reduction in seizure admissions in non-UK European countries after 2008, but we cannot be

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3 certain that there has not been a reduction in febrile convulsion admissions in continental countries
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5 which has been masked by a commensurate rise in non-febrile convulsion admissions.
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10 Our study was designed to describe but not to explain a change in admission incidence of FS. Our
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12 analysis was able to confirm that the fall in febrile seizure admissions was not due to cases being re-
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14 categorised as non-febrile seizures or fever with chills (two common differential diagnoses for FS),
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16 since there was no rise in non-febrile seizures or fever with chills at the same time as FS admissions
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18 fell. The analysis also demonstrated that in Scotland, the proportion of children admitted with a
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20 second, third or more febrile seizures was constant between 2001 and 2013 thus greatly reducing the
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22 possibility that the fall in febrile seizure admissions was be due to recurrent cases increasingly being
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24 managed in the community. There remains the possibility that cases are being increasingly managed
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26 in the community by parents and family practitioners but we believe this is unlikely since it is
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28 commonplace in the UK for an ambulance to be called when a child has their first febrile convulsion
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30 and the child brought to hospital urgently. Up to one third of children with a FS may have a
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32 recurrence[4] and the proportion of second FS admissions was typically 15-20% in our population and
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34 this is evidence that subsequent FS episodes are managed in the community. Whilst the number of
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36 FS admissions has fallen, the proportion of recurrent admission with FS has remained stable and this
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38 might indicate that fewer recurrent episodes of FS are managed in the community.
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45 When considering what might be causally linked to a fall in FS admissions in Scotland and England we
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47 thought that an abrupt change in host susceptibility (e.g. due to vaccination) was more likely than the
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49 sudden disappearance of a causative pathogen. Human herpes virus 6 is thought to precipitate many
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51 febrile seizures[6] but there was no plausible intervention in the UK which could have reduced this
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53 common infection. The 2006 introduction of routine infant pneumococcal vaccination was a
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55 reasonable candidate since it is feasible that any effect on febrile convulsions would only be seen after
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57 a lag during which the whole population is vaccinated and “herd immunity” is established.
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3 Furthermore pneumococcal vaccination is associated with a reduction in otitis media infections
4 [17,18] which are a common cause of FS[4]. Unfortunately FS data were not available in continental
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6 countries, and all seizure admission data following pneumococcal vaccination introduction were
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8 scarce. However there was no fall in all seizure admissions after the introduction of routine
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10 pneumococcal vaccination in Cyprus, Luxemburg or Switzerland. A further consideration is the type
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12 of pneumococcal vaccination which is delivered; the heptavalent vaccine introduced in the UK in 2006
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14 and was replaced in 2010 with a 13-valent vaccine and this change coincided with a change in
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16 empyema admissions[19] (commonly caused by pneumococcal serotypes).
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23 Further research into why FS admissions fell in the UK after 2008 could explore whether the
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25 prevalence of virulence of HHV6 (thought to be the major precipitant of FS) has changed. Other
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27 factors which might have contributed to a fall in FS include availability of antipyretics and public health
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29 initiatives which educate parents about the management of childhood fever. In the UK we know that
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31 all acute admissions rose between 2000 and 2013 [7,8], so changing practice in either primary or
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33 secondary care acute care seems unlikely to explain a reduction in FS admissions whilst other acute
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35 presentations rose.
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41 There are some further limitations which need to be considered when interpreting the results. First,
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43 as with all studies of routinely acquired data, there is the likelihood that in some cases the diagnostic
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45 code was not correct, for example FS may be coded as epilepsy but this will not change the secular
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47 trends we report here. There is a possibility that admissions with FS will have been coded as something
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49 other than the codes used to capture FS, non-febrile seizure or fever with chills and these admissions
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51 will have been missed in our analysis. Third, a more advanced approach to analysis such as spline
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53 analysis or interrupted time series analysis was not taken but the approach taken did allow our
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55 hypothesis to be tested and despite combining data from several years we were still able to see
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57 differences in febrile seizure admissions for Scotland and England.
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In summary, we have observed a fall of approximately 25% in febrile seizure admissions in Scotland and England since 2008. We cannot explain the reason for this fall.

Confidential: For Review Only

What is already known on this topic

The incidence of emergency paediatric medical hospital admissions rose between 2000 and 2013.

Contrary to the overall upwards trend, emergency admissions with all seizures (febrile and afebrile) fell between 2005/6 and 2015/16 in England.

What this study adds

There was a fall in hospital admissions for all seizures after 2008 in England and Scotland and this fall was explained by a fall in febrile seizures. There was no fall in all seizure admissions after 2008 in continental European countries. The reason for the fall in febrile seizure admissions is not clear.

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Table one. The absolute ("abs") number of annual admissions and standardised ("stand") annual incidence/1000 children of children with febrile seizures (International Classification of Diseases, ICD-10 code R56.0), non-febrile seizures (ICD-10 codes G40.3, G40.9 and R56.8) and fever with chills (ICD-10 code 50.9).

	Information Services Division (data from Scotland)						Hospital Episode Statistics (data from England)					
	Febrile seizure		Non febrile seizure		Fever with chills		Febrile seizure		Non febrile seizure		Fever with chills	
	abs	stand	abs	stand	abs	stand	abs	stand	abs	stand	abs	stand
2000	972	0.93	894	0.85	298	0.28	11,003	1.19	14,511	1.56	126	0.01
2001	1,036	1.00	1,050	1.01	321	0.31	11,600	1.26	14,446	1.56	124	0.01
2002	1,082	1.06	1,039	1.02	291	0.28	10,695	1.16	15,374	1.67	160	0.02
2003	1,151	1.14	1,210	1.20	418	0.41	11,986	1.31	14,844	1.62	167	0.02
2004	960	0.96	1,216	1.21	431	0.43	10,960	1.20	15,535	1.70	161	0.02
2005	1,189	1.19	1,212	1.22	476	0.48	11,381	1.25	16,495	1.81	221	0.02
2006	1,132	1.14	1,257	1.27	580	0.59	10,730	1.17	16,745	1.83	203	0.02
2007	1,148	1.16	1,104	1.12	636	0.64	10,323	1.12	16,859	1.83	278	0.03
2008	1,154	1.17	1,105	1.12	811	0.82	10,476	1.13	16,844	1.82	261	0.03
2009	1,036	1.05	1,134	1.15	855	0.87	8,784	0.94	16,567	1.78	279	0.03
2010	712	0.73	982	1.00	628	0.64	9,002	0.96	16,758	1.79	322	0.03
2011	737	0.75	1,030	1.04	573	0.59	8,548	0.90	17,182	1.81	333	0.03
2012	674	0.69	942	0.97	457	0.47	8,736	0.92	16,960	1.79		
2013	688	0.71	1,086	1.12	490	0.50	8,348	0.87	17,297	1.81		

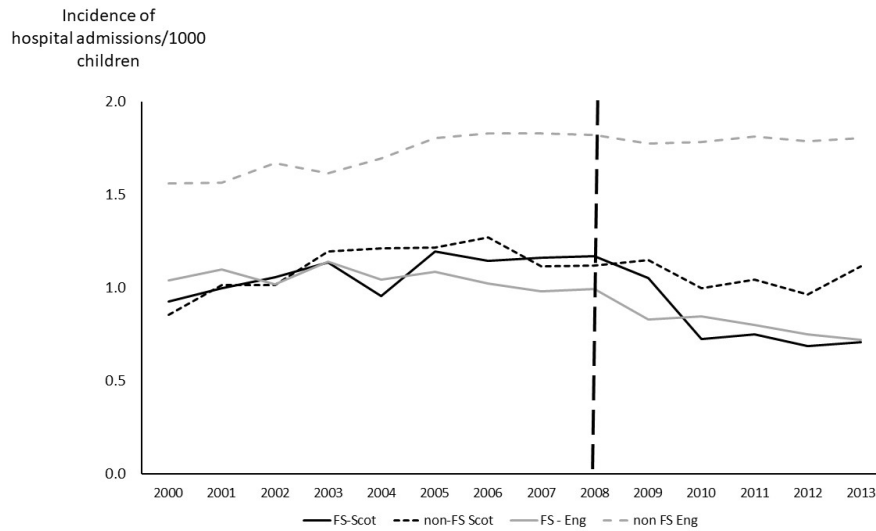
Table two. Mean (standard deviation) incidence of admissions for all seizures (defined as ICD-10 code R56) in eleven European countries for the periods 2000-2008 and 2009-2013. Data from Denmark were only available 2003-2006 and are not shown.

Country (data available from-to)	Mean (SD) incidence of admissions for all seizures/1000 children aged <5 years, n=number of year's data	
	Up to and including 2008	2009 onwards
Croatia (2002-2013)	8.9 (1.6) n=7	11.1 (0.3) n=5
Cyprus (2004-2012, not 2010)	3.6 (1.1) n=5	3.2 (0.4) n=3
Finland (2001-2012, not 2005-6)	5.4 (0.6) n=6	4.1 (0.4) n=4
Latvia (2004-2012)	0.9 (0.1) n=5	1.0 (0.2) n=4
Lithuania (2001-2012)	0.7 (0.3) n=8	1.4 (0.8) n=4
Luxembourg (2002-2012)	4.8 (0.7) n=7	5.2 (2.4) n=4
Malta (2006-2012)	5.7 (0.3) n=3	6.6 (0.5) n=4
Poland (2003-2012)	3.1 (0.8) n=6	1.6 (0.1) n=4
Slovakia (2002-2011)	6.7 (1.0) n=7	5.9 (0.9) n=4
Slovenia (2004-2012, not 2006-7)	11.4 (1.8) n=3	7.3 (3.2) n=4
Switzerland (2002-2012)	3.9 (0.3) n=7	3.8 (0.8) n=4
United Kingdom (2000-2011)	7.1 (0.7) n=9	5.2 (0.1) n=3

FIGURE LEGENDS

Figure one. Incidence of admission per 1000 children with febrile seizures (FS) and non-febrile seizures (non-FS) in Scotland and England. The denominator for Scotland admissions was children aged ≤ 16 years and for England was children aged ≤ 14 years. The vertical broken line indicates the time after which admissions for febrile seizures was noted to have changed in Scotland.

Figure two. The incidence of all seizure admissions (i.e. with an ICD-10 code beginning R56) in 13 European countries. The denominator is all children aged \leq four years and the incidence is therefore higher than for figure one. The vertical broken line indicates the time after which admissions for febrile seizures was initially noted to have changed in Scotland and England.



25 Figure one. Incidence of admission per 1000 children with febrile seizures (FS) and non-febrile seizures
 26 (non-FS) in Scotland and England. The denominator for Scotland admissions was children aged ≤ 16 years
 27 and for England was children aged ≤ 14 years. The vertical broken line indicates the time after which
 28 admissions for febrile seizures was noted to have changed in Scotland.

29 338x190mm (96 x 96 DPI)

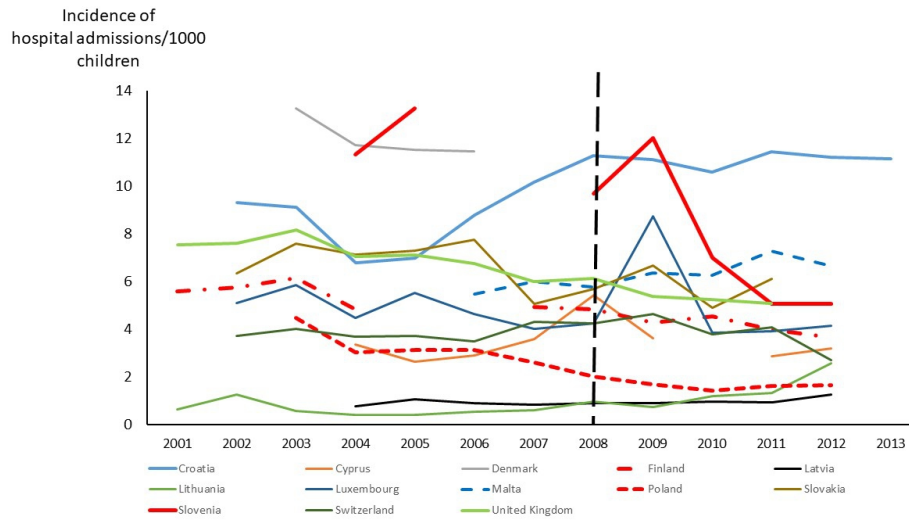


Figure two. The incidence of all seizure admissions (i.e. with an ICD-10 code beginning R56) in 13 European countries. The denominator is all children aged \leq four years and the incidence is therefore higher than for figure one. The vertical broken line indicates the time after which admissions for febrile seizures was initially noted to have changed in Scotland and England.

338x190mm (96 x 96 DPI)

Supplementary table one. The number of individual children with any and more than one admission to hospital in Scotland for febrile seizure between 2000 and 2013.

	The number of individual children with any febrile convulsion admission between 2000-2013	The number of children admitted for febrile convulsion on >1 occasion between 2000-2013 (sum of admissions for these individuals)	Percentage of all febrile seizure admissions where there had previously been an admission for febrile seizure
2000	903	60 (69)	7%
2001	892	107 (144)	12%
2002	892	150 (190)	17%
2003	939	148 (212)	16%
2004	754	143 (206)	19%
2005	940	154 (249)	16%
2006	876	158 (256)	18%
2007	936	146 (212)	16%
2008	942	136 (212)	14%
2009	811	150 (225)	18%
2010	571	89 (141)	16%
2011	585	104 (152)	18%
2012	546	88 (128)	16%
2013	568	81 (120)	14%

Supplementary table two. Admission incidence for all seizure admissions in children aged ≤ 4 years in 13 European countries. The incidence in bold and underlined indicates the year when routine pneumococcal vaccination was introduced in that country. The incidences in boxes with grey back ground were compared with incidences in earlier years for that country for the analysis in table 2 in the main paper.

	Croatia	Cyprus	Denmark	Finland	Latvia	Lithuania	Luxembourg	Malta	Poland	Slovakia	Slovenia	Switzerland	United Kingdom
2000													7.415
2001				5.5992		0.636							7.5353
2002	9.3194			5.7427		1.2654	5.0949			6.3487		3.7118	7.6132
2003	9.1354		13.2801	6.1442		0.552	<u>5.8609</u>		4.4827	7.5847		4.0013	8.1772
2004	6.7922	3.3693	11.7482	4.8506	0.7533	0.4014	4.4794		3.0169	7.1392	11.3355	3.6926	7.0615
2005	6.9704	2.6492	11.5244		1.0535	0.3921	5.532		3.1105	7.2835	13.277	3.7128	7.1312
2006	8.7778	2.9124	11.4794		0.8894	0.5183	4.6263	5.48	3.1278	7.7517		<u>3.499</u>	<u>6.7416</u>
2007	10.171	3.5761		4.9453	0.8181	0.5919	4.0169	6.001	2.6109	5.05		4.3104	5.9956
2008	11.288	<u>5.4137</u>		4.8312	0.8985	0.9637	4.248	5.7624	2.0007	5.6965	9.7017	4.256	6.1363
2009	11.1343	3.6205		4.2619	0.8841	0.7139	8.7294	6.348	1.6894	<u>6.6742</u>	12.0322	4.6242	5.3654
2010	10.6053			<u>4.5479</u>	<u>0.9491</u>	1.1767	3.8447	6.2765	<u>1.4286</u>	4.9002	6.99	3.792	5.2358
2011	11.4425	2.8579		3.9862	0.942	1.3081	3.8995	7.2662	1.6187	6.1159	<u>5.0728</u>	4.07	5.0966
2012	11.2134	3.1862		3.6595	1.2661	2.5586	4.1288	6.6568	1.6599		5.0728	2.7096	
2013	11.1518												

Supplementary table three. Mean (standard deviation) incidence of admissions for all seizures (defined as ICD-10 code R56) in eleven European countries for the period beginning three years after the introduction of routine vaccination and earlier years. Data from Denmark were only available 2003-2006 and are not shown. In the general estimating equation there was a non-significant fall in seizure admission incidence/1000 with a three year lag after pneumococcal vaccination was introduced (0.46 [95% CI -0.18, 1.09] p=0.157)

Country (data available from-to)	Up to and including two years after pneumococcal vaccination introduced	Three years after vaccination introduced
Croatia (2002-2013)	No routine vaccination	
Cyprus (2004-2012, not 2010)	3.6 (1.0) n=5	3.0 (0.2) n=2
Finland (2001-2012, not 2005-6)	Vaccination introduced 2010	
Latvia (2004-2012)	Vaccination introduced 2010	
Lithuania (2001-2012)	No routine vaccination	
Luxembourg (2002-2012)	5.2 (0.6) n=4	4.8 (1.8) n=7
Malta (2006-2012)	No routine vaccination	
Poland (2003-2012)	Vaccination introduced 2010	
Slovakia (2002-2011)	Vaccination introduced 2009	
Slovenia (2004-2012, not 2006-7)	Vaccination introduced 2011	
Switzerland (2002-2012)	3.9 (0.3) n=7	3.8 (0.8) n=4
United Kingdom (2000-2011)	7.1 (0.7) n=9	5.2 (0.1) n=3